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TOWNSEND AND TOWNSEND AND CREW, LLP			LUNDGREN, JEFFREY S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/627,592	Applicant(s) VANDER HORN, PETER B.	
	Examiner Jeffrey S. Lundgren	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 July 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 6-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/18 and 7/6</u> | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Application Reassigned

Applicants are informed that this application has been reassigned to Examiner Jeff Lundgren in Art Unit 1639; for more efficient processing of the application, all correspondence from Applicants should reflect these changes where appropriate.

Election/Restrictions

Claims 6-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on July 1, 2005.

Accordingly, claims 1-5, along with the elected enzyme species "polymerase" and elected biological activity "extension," will be examined on the merits. Claims 6-16 are withdrawn from consideration.

This restriction requirement is final.

Objection to the Abstract

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

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Where applicable, the abstract should include the following:

- (1) if a machine or apparatus, its organization and operation;
- (2) if an article, its method of making;
- (3) if a chemical compound, its identity and use;
- (4) if a mixture, its ingredients;
- (5) if a process, the steps.

Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "the wild-type proteins" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christians *et al.*, *Nature Biotechnology* 17:259-264 (1999), and any single disclosure or combination of Farinas *et al.*, *Current Opinions in Biotechnology* 12(6):545-551 (2001), Gibbs *et al.*, *Gene* 271:13-20 (2001), and Joern *et al.*, *Journal of Molecular Biology* 316:643-656 (2002).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The limitations of claim 1 are compared to the teachings of Christians in the table below:

§	<i>Claim 1</i>	<i>Christians</i>
A	A method of creating hybrid proteins having a common biological activity comprising the steps of:	"We used the DNA family shuffling method to create a library of HSV-1/HSV-2 TK chimeras, which were tested in a high-throughput robotic screen to identify clones capable of sensitizing <i>Escherichia coli</i> to AZT. Clones with improved function were reshuffled and rescreened for a total of four cycles to evolve chimeras with greatly enhanced activity on AZT." (Christians, at page 259, col. 2);
B	(a) creating a library comprising 32 or more nucleic acids encoding a plurality of hybrid protein members, wherein the members differ from a set of at least two parent proteins with corresponding amino acids, and	four generations of hybrids were created from the two parents as reported in Table 1 with each generation being at least 32; and "For the fourth cycle we used a mixture of the 33 best clones from cycle 3, doped with a 10-fold smaller amount of DNA from the next best clones" Christians, at page 260;
C	i. where the parent proteins are homologous proteins having greater than 60% amino acid similarity to each other and having at least one common biological activity,	see Figure 2(a)-(c), Christians, at page 261, where greater than 80% amino acid similarity is illustrated;
D	ii. where a majority of the library members have a greater than 60% amino acid similarity to any of the parent proteins, and	see Figure 2(a)-(c) Christians, at page 261; "The deduced protein sequence of cycle 3 TK shows that it is 94% identical to HSV-1 TK (22 differences) and 77% identical to HSV-2 TK (86 differences). The sequence of cycle 4 TK is quite similar to that of cycle 3 TK (98% identical) but with some different crossovers and some different point mutations. At least 10 DNA crossover events occurred during the four rounds of shuffling to create cycle 4 TK. One crossover could be pinpointed to 1 bp (Fig. 2C) and another to 3 bp, demonstrating that fine-grained recombination is achievable by DNA shuffling. Such crossovers are made possible by flanking homology. Three of the point mutations (Y101H, R176W, and M179V) found in both enzymes are in the active site (see below)." Christians, at pages 260-261.

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§	Claim 1	Christians
E	iii. where the majority of differences between the library members and the parent proteins are confined to those corresponding amino acids that differ among the parent proteins;	see Figure 2(a)-(c), and description thereof, Christians, at page 261 (note the majority of the differences);
F	(b) expressing protein from at least one library member to create at least one hybrid protein, (c) selecting at least one protein having a common biological activity of the parent proteins.	see <i>Family shuffling and screening</i> , Christians, pages 259-260; many of the proteins/clones are expressed and demonstrate common biological activity to either or both of the parents in all of the four generations/cycles; see Tables 1 and 2, Christians, at page 260.

As noted from the table above, Christians teaches a method for creating hybrid proteins having a common biological activity by family shuffling (i.e., “homologous genes are mixed, randomly fragmented, and recombined using conditions that permit annealing and extension of nonidentical complementary strands,” Christians, at page 259, col. 1), in particular, to create a library of HSV-1/HSV-2 TK chimeras. Christians states the advantages of family shuffling:

“This use of functional diversity, in the form of related genes already subjected to millions of years of natural selection, bypasses the limitations of natural species barriers and allows rapid searching of large and diverse regions of sequence space. DNA family shuffling has been used to evolve β -lactamase from four starting genes⁶ and biphenyl dioxygenase from two genes⁷.”

Id., at page 259, col. 1.

However, Christians does not explicitly disclose that the “majority of the library members have a greater than 60% amino acid similarity to any of the parent proteins.”

Farinas provides a review article on directed enzyme evolution for industrial and research applications. Farinas teaches that the strategy of directed evolution generally involves iterations of mutagenesis or recombination to form a library, followed by a screening or selection process, as also taught in Christians. One technology taught by Farinas to be useful for producing enzymes with enhance properties includes *in vitro* recombination by DNA shuffling. Regarding what is generally well-known in the art, Farinas teaches the importance of sequence similarity:

“All the available methods for DNA shuffling require high sequence similarity for recombination (> ~60%).”

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Farinas, at page 548, col. 2. Further evidence that those of ordinary skill in the art appreciate the fact that high sequence similarity is desirable and well-known for optimizing chimeras with enhanced activity is demonstrated by Gibbs:

“If sequence similarity is low between the input genes, the majority products tend to be the reassembled parental genes and extensive searches need to be carried out to find chimeric recombinants [citation omitted].”

Gibbs, at page 13, col. 2. Further evidence of this understanding is provided by Joern:

“Family shuffling represents a potentially powerful approach to generating novel sequences that encode functionally interesting proteins. Even when the homologous parent proteins differ at a large number of amino acid residues (as much as 30 or 40 %), a significant fraction of the resulting chimeric proteins retain some level of function.”^{4,6,16,}

Joern, at page 643, col. 1. In other words, Joern teaches that parents may have as low as 70% or 60% amino acid similarity.

Claim 2 further requires that the parent proteins are enzymes, and claim 3 further requires that the parent proteins are isozymes.

As already noted above, Christians teaches the parent proteins are enzymes/isozymes (*i.e.*, HSV-1 and -2 thymidine kinases; see *Abstract*).

Claim 5 further requires that the parent proteins have greater than 80% amino acid similarity, and the majority of the library members have greater than 80% amino acid similarity to any of the wild-type proteins.

As explained above for Christians, the parent proteins have greater than 80% amino acid similarity. Furthermore the advantages of using highly similar parent sources is well-known and understood, as already evidenced by Farinas and Gibbs. Christians also demonstrates the production of chimeras having high amino acid similarity to the parents, *i.e.*, at the 80% level (see table above).

Accordingly, applying this understanding as a selection criteria in the art of directed evolution using homologous parent proteins, one of ordinary skill in the art would have recognized the advantages of using sequences with either of 60% or 80% amino acid similarity between the two parent proteins, and 60% or 80% amino acid similarity between a majority of

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the library members and any parent protein. The nature of the art often involves reiterations, or multi-generation directed evolution to produce an effective chimera or chimera library. In the teachings of Christians, four generations were produced. One of ordinary skill in the art would reasonably expect that by maintaining a high degree of similarity between a majority of the library members and any of the parent proteins would be required to maintain and enhance the specificity and activity of the newly evolved enzymes as one advances through subsequent generations of chimeras. Applicants' disclosure neither contains nor suggests anything unexpected in view of what is taught by either Christians, Farinas, Gibbs, or Joern, in particular, with regard to the specific similarity between the parent proteins and the majority of the library members. The art clearly establishes the advantages of producing chimeras from parents having a higher degree of amino acid similarity. Therefore, one of ordinary skill in the art would have found the invention *prima facie* obvious at the time it was invented in view of the cited art.

Claims 1-5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Christians, Farinas, Gibbs, and/or Joern as applied to claims 1-3 and 5 above, and Xia *et al.*, *PNAS* 99(10):6597-6602 (2002).

Claim 4 further requires that the parent proteins are polymerases.

None of Christians, Farinas, Gibbs, or Joern, teach using at least two parent polymerases for producing polymerase chimeras.

Xia teaches a method for identifying polymerases that have been selectively mutated for enhanced activity using an activity-based selection method, in which a DNA polymerase and its substrate are both attached to the minor coat protein of a phage. Xia teaches that *in vitro* evolution is a powerful tool for generating the library of polymerase, wherein any number of approaches can be used prior to Xia's screening process, including, "cassette mutagenesis (1, 2), error prone PCR (3, 4), staggered extension process PCR (5), and gene shuffling (6, 7)." Xia, at page 6597, col. 1. The benefits of producing novel and improved polymerase are stated:

"The manipulation of DNA polymerase activity has attracted a great deal of attention because of the central roles of polymerases in biological processes as well as their utility in biotechnology applications. Earlier efforts to modify polymerase activity have focused largely on the rational design of site-directed mutants. For example, significant effort has been

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directed toward mutagenizing a DNA polymerase into an RNA polymerase (RNAP) (12, 13). Mutants that extend DNA primers by the incorporation of single ribonucleoside triphosphates (rNTPs) have been constructed; however, mutants that efficiently add successive rNTPs have proven more difficult to isolate. Moreover, in all reported cases, the mutant enzyme still prefers the dNTP substrates. The limited success of the rational approach likely results from the limited sequence space of the polymerases examined in these experiments. In vitro evolution strategies in which large populations of mutants are sampled for those with the desired activities are more likely to be successful, especially for rare activities.”

Xia, at page 6597, col. 1.

One of ordinary skill in the art would have been motivated by the teachings of Christians, in view of Farinas Gibbs, and/or Joern, to prepare a library of chimeras from at least two homologous polymerases as taught by Xia, because of the advantages of Christians’ method for improved directed evolution *via* family shuffling. One of ordinary skill in the art would have appreciated the advantages of using parent proteins having high homology, as taught by Farinas Gibbs, and/or Joern, because it is understood in the art that a certain level of amino acid similarity between the parents is required for producing a library of active proteins through chimeragenesis. As communicated in the previous rejection, those in the art recognize that a higher degree of homology should be retained between parents, and between parents and offspring proteins, because of the reiterative nature of *in vitro* evolution, and the correlation between successful chimeras and their homology relationship to their parents. One would reasonably expect that the teachings of Christians, Farinas, Gibbs, and Joern, would provide a successful method for generating a library of chimeric polymerase to be screened using Xia’s phage display method. Accordingly, claim 4 does not distinguish over the art of record, and is found to be *prima facie* obvious.

Conclusions

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the

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amendment is not supported *in ipsius verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached on 8:30 AM to 5:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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